

FOOD AND DRUG ADMINISTRATION (FDA)

Center for Drug Evaluation and Research (CDER)

Joint Meeting of the Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC) and the Ophthalmic Devices Panel of the Medical Devices Advisory Committee (OP-MDAC)

FDA White Oak Campus, Building 31, the Great Room (Rm. 1503)

White Oak Conference Center, Silver Spring, Maryland

February 24, 2015

DRAFT QUESTIONS

1. **DISCUSSION:** Please discuss and comment on the following Study Design Elements:

Planned Enrollment and Size of Studies

- -160 patients (80 per arm) originally planned in the studies below versus actual enrollment
- - Size of Safety database

	CXL	Sham
UVX-001 and -002 Progressive Keratoconus	102	103
UVX-001 and -003 Corneal Ectasia	91	88

2. **DISCUSSION:** For both proposed indications, the studies were to evaluate efficacy three months after treatment as reflected by the protocol-defined primary endpoint. For the progressive keratoconus population, statistical significance was not achieved at Month 3. Statistical significance was achieved at Month 3 for the corneal ectasia population. The Statistical Analysis Plan submitted after the last patient visit extended the evaluation of efficacy to Month 12, and the subsequent analysis used a last observation carried forward (LOCF) strategy to impute missing data resulting from patient withdrawal as well as to impute data for sham subjects receiving CXL treatment at Month 3 or 6. Please discuss the strengths and weaknesses of the trial design and analysis including the effect of the following on your evaluation of product efficacy:

- Potential introduction of bias
- Number of subjects available
- Use of LOCF
- Stability of corneal response to treatment

3. **DISCUSSION:** In these studies, at the time of treatment there were the following number of pediatric patients enrolled (stratified by ≤ 21 years CDRH and ≤ 16 years CDER) :

	CXL	Sham
Keratoconus ≤ 21 years	19	14
Keratoconus ≤ 16 years	6	4
Corneal ectasia ≤ 21 years	0	0
Corneal ectasia ≤ 16 years	0	0

For the proposed indication for progressive keratoconus, please discuss:

- What is the minimum age supported by the data
- Applicability of extrapolation from adult data?

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DRAFT QUESTIONS (cont.)

4. **DISCUSSION:** Please discuss your Interpretation of Endothelial Cell Count Findings (See endothelial cell count tables).
5. **DISCUSSION:** The studies were conducted on a different device (the IROC UV-X) than the one proposed to be marketed (KXL System). Differences include (but are not limited to):
 - Illumination diameter (aperture)
 - UV focal alignmentIn light of the differences and lack of any data collected using the KXL System, please discuss the adequacy of the current dataset to assess safety and efficacy of the KXL System.
6. **DISCUSSION:** Please discuss your recommendations regarding the need for analyses (if any) on the additional data that had been collected during the clinical trials to adequately characterize the safety and efficacy profile of this combination product.
7. **DISCUSSION:** Please discuss any potential safety issues.
8. **DISCUSSION:** The applicant proposes indication of progressive keratoconus. Please discuss applicability of extrapolation to general keratoconus population
9. **VOTE:** Has substantial evidence of efficacy and safety been demonstrated for the drug-device combination of Photrexa Viscous and Photrexa (riboflavin ophthalmic solution) and the KXL System (UVA light) to support approval for progressive keratoconus? Yes/No
 - a. If yes (recommend approval), do you have any suggestions regarding the draft labeling of the product?
 - b. If the product is recommended for approval are additional studies needed post-approval? If so, please comment on type of study; e.g., objectives, population, endpoints, duration, design.
 - c. If the product is not recommended for approval because additional studies are needed, please comment on the types of study(ies) that are needed.

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DRAFT QUESTIONS (cont.)

10. **VOTE:** Has substantial evidence of efficacy and safety been demonstrated for the drug-device combination of Photrexa Viscous and Photrexa (riboflavin ophthalmic solution) and the KXL System (UVA light) to support approval for corneal ectasia following refractive surgery? Yes/No
- a. If yes (recommend approval), do you have any suggestions regarding the draft labeling of the product?
 - b. If the product is recommended for approval are additional studies needed post-approval? If so, please comment on type of study; e.g., objectives, population, endpoints, duration, design.
 - c. If the product is not recommended for approval because additional studies are needed, please comment on the types of study(ies) that are needed.